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ORIGINAL ARTICLE

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Long-term enteral nutrition in infants and young children with chronic renal failure

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Abstract An inadequate nutritional intake is common in infants and young children with chronic and end-stage renal failure (CRF/ESRF), causing poor weight gain and growth retardation. In a programme of enteral feeding (EF), growth, nutritional intake and outcome for oral feeding were evaluated in 35 children with CRF/ESRF, mean (range) age 1.6 (0–4.9) years at start of EF for 30 (12–60) months. Twenty-nine had a glomerular filtration rate of 12.1 (6–26) ml/min per 1.73 m^2 and 6 were on peritoneal dialysis. Mean (SD) weight standard deviation scores (SDSs) in the 0 to 2-year age group (n=26) were –3.3 (1.0) 6 months before EF, –3.1 (1.3) at the start, –1.7 (1.4) at 1 year, (P=0.0003) and –1.4 (1.8) at 2 years, (P=0.0008). Height SDSs were –2.9 (0.7), –2.9 (1.2), –2.2 (1.2) (P=0.008) and –2.1 (1.3) (P=0.004). Weight SDSs in the 2 to 5-year age group (n=9) were –2.3 (1.2), –2.0 (1.1), –1.1 (1.3) (P=0.002) and –0.9 (1.0) (P=0.04). Height SDSs were –2.8 (0.6), –2.3 (0.7), –2.0 (0.7) and –2.0 (0.8). There was no change in energy intake as a percentage of the estimated average requirement, nor was this exceeded. Percentage energy from the EF in the 0 to 2 year age group remained unchanged despite an absolute increase in energy intake with age. Twenty-one have had renal transplants, of whom 86% eat and drink normally. Long-term EF prevents or reverses weight loss and growth retardation in children with CRF/ESRF, with the achievement of significant catch-up growth if started before age 2 years.

Key words Chronic renal failure · Childhood chronic renal failure · Linear growth · Nutrition · Enteral feeding · Energy intake · Protein intake

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Introduction

The difficulties associated with feeding the infant and young child with chronic or end-stage renal failure (CRF/ESRF) are well recognised. Refusal of feeds, reduced spontaneous oral intake and vomiting result in failure to provide an adequate nutritional intake and, although other factors have been implicated in the growth failure associated with CRF, i.e. renal osteodystrophy, acidosis, salt wasting and anaemia, an adequate energy intake is probably critical. As growth velocity is both maximal but declining in infancy, the magnitude of growth loss and growth potential is greatest during this time, so prevention and treatment should be directed towards these early phases of growth [1–3]. However in practice it is often difficult to provide a "safe" nutritional intake and variable results have been reported with either oral energy supplements or enteral feeding (EF) [4–7]. Previous studies have clearly shown an inadequate spontaneous energy intake in children with CRF without intervention and a protein intake which exceeds the recommended dietary allowance (RDA) without specific dietary advice [8, 9]. EF has been an integral part of the care of infants and children with CRF/ESRF at Great Ormond Street Hospital for Children since 1989, and this study retrospectively describes our long-term experience of EF, evaluating weight gain and linear growth, nutritional intake, biochemical parameters and outlook for normal feeding.

Patients and methods

Thirty-five children (8 girls) with CRF/ESRF commenced EF for any one or more of the following indications; failure to maintain expected weight gain despite the use of energy supplements, recurrent vomiting and parental stress. They were included in the study if they had completed at least 12 months of EF. Their diagnoses were renal dysplasia [20], posterior urethral valves [9], occult neuropathic bladder with reflux nephropathy [1], congenital nephrotic syndrome [1], cortical necrosis [1], interstitial nephritis [2] and bilateral Wilms tumour [1]. In addition 6 children had major co-morbid conditions: 4 had congenital heart disease requiring major surgery in the first 4 months of life (coarctation of the aorta,

ventricular septal defect, total anomalous pulmonary venous drainage and complex cyanotic heart disease), 1 had the CHARGE association [10] and 1 microcephaly associated with severe developmental delay. The mean age at the start of EF was 1.6 (0–4.9) years, with 26 children aged 0–2 years (10 <0.5 and 3 0.5–1 years) and 9 children aged 2–5 years. Twenty-nine were conservatively managed with a mean glomerular filtration rate of 12.1 (6–26) ml/min per 1.73 m^2 and 6 were established on peritoneal dialysis (PD), 3 aged 0–2 years. The mean plasma creatinine in the conservatively managed group was 237 µmol/l (SD 117) at the start and 392 µmol/l (SD 244) at the end of the study.

The mean duration of feeding was 30.8 (range 12–60) months, defined as the last point of assessment if EF continued or completion of the study due to a change of treatment modality, prescription of growth hormone (GH) or a return to full oral feeding. Reliable data were available in 13 children (6 aged 0–2 years) 12 months before and 21 children (14 aged 0–2 years) 6 months before the start of EF. All 35 completed the assessment at 1 year and 23 at 2 years (16 aged 0–2 years). Concomitant medical management included correction of metabolic acidosis with sodium bicarbonate, salt supplementation if clinically indicated, control of secondary hyperparathyroidism using calcium carbonate as a phosphate binder and 1-α-hydroxyvitamin D_3 and correction of anaemia with subcutaneous recombinant human erythropoietin. Four children were on continuous cycling PD overnight, 1 used continuous ambulatory PD and 1 both modalities.

Twenty children were fed using a nasogastric tube (NGT), 1 by percutaneous endoscopic gastrostomy (PEG) and 1 by gastrostomy (having had a Nissen's fundoplication). Six converted from a NGT to a PEG during the study. Six NGT-fed children subsequently required a Nissen's fundoplication and gastrostomy; 5 for persistent vomiting and 1 as part of the procedure for gastrostomy formation. One child needing a fundoplication had a PEG left in place. Feeds were delivered continuously overnight using an automated pump with additional daytime boluses as necessary. Oral stimulation continued to be encouraged with, where possible, the introduction of age-appropriate foods, inclusion of the child at mealtimes, prohibition of force feeding and use of pacifiers. The dietary aims were to provide at least 100% of the estimated average requirement (EAR) for energy for chronological age and at least 100% of the reference nutrient intake (RNI) for protein for height age, based on the dietary reference values for food, energy and nutrients for a normal population (UK 1991) [11]. To achieve these aims feeds were individually prescribed, but were based on a whey-dominant infant formula (SMA Gold, Cow and Gate Premium, Kindergen PROD) in the children <2 years and a whole-protein enteral feed (Clinifeed ISO, Nepro) in those >2 years supplemented with energy: either a glucose polymer (Super Soluble Maxijul, Caloreen) alone or in combination with a long-chain fat emulsion (Calogen), or a combined fat and carbohydrate product (Duocal).

The children were seen monthly in the CRF/PD clinic for review by the same team, i.e. doctor, dietitian and clinical nurse specialist before and after starting EF. The weight (unclothed) and height (supine <2 years) and results of routine biochemistry were recorded in the clinical notes. A record of current dietary intake was taken at each clinic visit and if oral intake was significant parents were asked to recall the last 3 days for subsequent computer analysis (Diet 2000). Relevant data, including height, weight, plasma urea, albumin and intact parathyroid hormone (PTH) levels (from March 1989), assessed total energy and protein intake, percentage of energy and protein energy derived from the feed, concentration of carbohydrate and fat in the feed, were then extracted at 1 year and 6 months before EF, at the start of EF and then at yearly intervals. The height and weight were expressed as standard deviation scores (SDSs) calculated from the formula: SDS=measured height – mean height for age / SDS according to normal population data [12]. The long-term outcome for oral feeding was recorded.

Statistical analysis

The values are expressed as mean and SD. The data were compared for each age group before the start of EF and at 1 and 2 years by a paired *t*-test and a two-sample *t*-test where appropriate. A statistical difference was considered significant if a *P* value of <0.05 was obtained.

Results

Growth

The change in weight and height. SDS for each individual before and after starting EF is shown in Fig. 1a and b.

Weight 0–2 years

The mean weight SDS at 12 and 6 months before EF was –3.1 (0.8) and –3.3 (1.0), respectively and at the start of

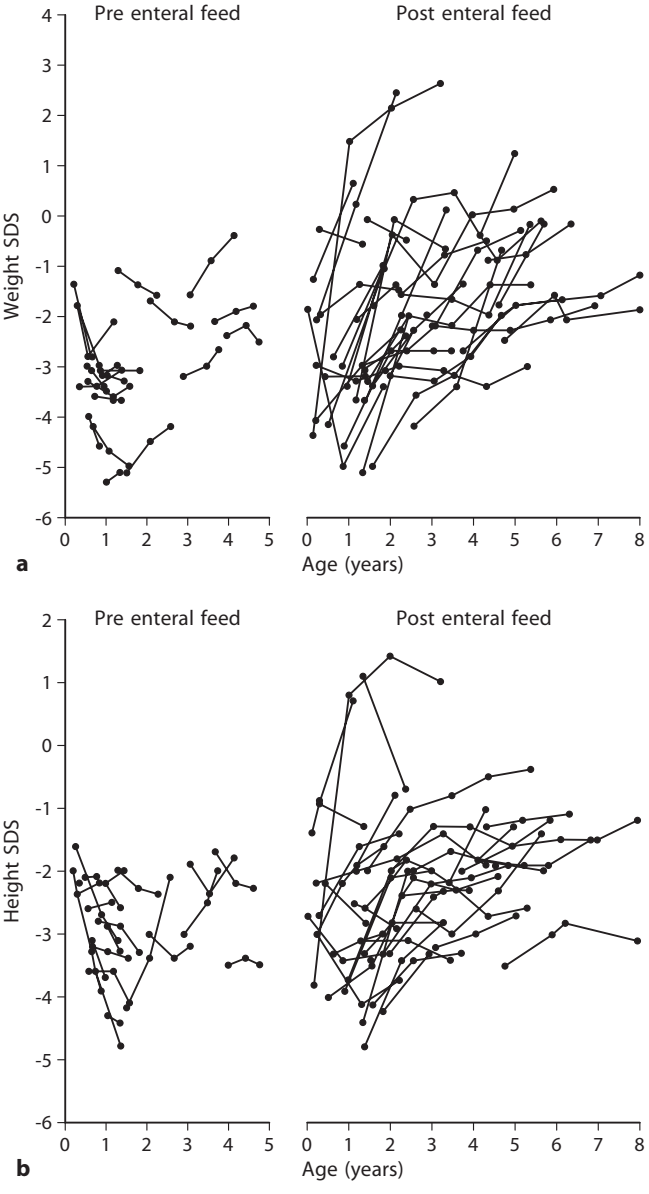

Fig. 1 a Individual weight standard deviation score (*SDS*) and **b** height SDS for age before and after starting enteral feeding

Table 1 Assessed energy intake for children in both age groups (*EAR* estimated average requirement)

	% EAR (total intake)		% Energy from feed	
	0–2 years	2–5 years	0–2 years	2–5 years
6 months pre	93.7 (23.2)	81.4 (21.6)		
Start	104.2 (26.2)	96.4 (14.9)	82.1 (23.7)	51.8 (20.9)
1 year	102.3 (15.3)	85.6 (18.3)	80.4 (20.4)	61.1 (21.3)
2 years	96.5 (16.3)	88.1(18.5)	78.9 (21.5)	61.3 (21.1)

Table 2 Concentration of energy supplements in feed in children of both age groups

	% Fat		% Carbohydrate		Non-protein energy (kcal/100 ml)	
	0–2 years	2–5 years	0–2 years	2–5 years	0–2 years	2–5 years
Start	4.5 (1.0)	4.5 (1.4)	15.6 (4.5)	17.0 (5.7)	103.1 (22.9)	108.6 (31.8)
1 year	4.8 (1.2)	4.9 (1.7)	19.9 (4.6)	21.9 (6.9)	122.3 (26.6)	132.1 (31.6)
2 years	4.8 (1.5)	5.2 (1.9)	21.4 (5.5)	26.5 (6.2)	129.0 (25.6)	153.0 (33.8)

Table 3 Assessed protein intake in children of both age groups

	%RNI (total intake)		% Protein energy from feed	
	0–2 years	2–5 years	0–2 years	2–5 years
6 months pre	113.2 (13.5)	166.3 (37.1)		
Start	110.2 (31.6)	157.0 (25.7)	6.4 (1.8)	6.6 (1.2)
1 year	110.0 (30.1)	172.8 (64.0)	5.3 (1.4)	7.9 (2.4)
2 years	117.3 (39.9)	172.4 (84.9)	5.6 (1.5)	7.4 (2.9)

EF was –3.1 (1.3). The SDS increased at 1 year to –1.7(1.4) (P=0.0003) and at 2 years to –1.4 (1.8) (P=0.0008).

Weight 2–5 years

The mean weight SDS at 12 and 6 months before EF was –2.5 (1.3) and –2.3 (1.2), and at the start was –2.0 (1.1). The SDS increased at 1 year to –1.1 (1.3) (P=0.002) and at 2 years to –0.9 (1.0) (P=0.04).

Height 0–2 years

The mean height SDS at 12 months and 6 months before EF was –2.6 (0.7) and –2.9 (0.7), and at the start was –2.9 (1.2) (P=0.005). The SDS increased at 1 year to –2.2 (1.2) (P=0.008) and at 2 years to –2.1 (1.3) (P=0.004).

Height 2–5 years

The mean height SDS at 12 and 6 months before EF was –2.8 (0.9) and –2.8 (0.6) and at the start of feeding was –2.3 (0.7). There was no significant increase in the SDS after 1 year, –2.0 (0.7), or at 2 years, –2.0 (0.8).

Diet

The results of the dietary analysis for energy intake for each age group are shown in Tables 1 and 2 and for protein intake in Table 3, excluding the 6 children on PD.

Energy

The assessed mean energy intake as a percentage of the EAR did not change significantly in either age group 6 months before, at the start or at 1 and 2 years of EF. The percentage energy from the EF did not change with time in the 0 to 2 years age group. In the 2 to 5-years group the percentage energy from EF increased at the 1 year assessment (P=0.03), but not at 2 years. The percentage energy from the EF was significantly greater in the 0- to 2-years group at the start (P=0.002) and at 1 year (P=0.02) compared with the older group.

The percentage fat concentration tolerated in the feed remained constant in both age groups throughout the study. The percentage carbohydrate concentration tolerated increased significantly in the 0 to 2-years group after 1 year (P=0.001) and 2 years (P=0.001), and in the 2 to 5-year age group at 2 years (P=0.04). There was a trend towards improved tolerance of a greater carbohydrate concentration in the older children by 2 years. The total non-protein energy content of the feed did not differ between the age groups, but increased significantly by 2 years in both the 0 to 2-year group (P=0.0002) and the 2 to 5-year group (P=0.04).

Protein

There was no change before or during the study in the percentage RNI for protein in either age group of the conservatively managed children. The percentage RNI was significantly higher in the 2 to 5-year group before, at the start and at 1 year (P=0.0004, 0.003 and 0.002). The percentage protein energy from the feed was less at both 1 year and 2 years compared with the initial feed (P=0.01 and 0.05) in the 0 to 2-year group, but remained constant in the older group. At 1 year the percentage protein energy was significantly higher in the older children (P=0.002).

Biochemistry

The mean plasma urea in the conservatively managed children was 15.5 (8.6) mmol/l at the start of EF, 17.8 (7.4) at 1 year and 17.8 (7.8) at 2 years (NS) and the plasma albumin increased from 37.4 (4) g/l at the start of EF to 40.3 (3.9) at 1 year (P=0.002) and 39.3 (3.5) at 2 year (P=0.02). The intact PTH was within twice the normal range (5–45 ng/l or 1–6.5 pmol/l) in 65% (n=29) of the children at the start of EF, in 86% (n=35) at 1 year and 87% (n=24) at 2 years.

Outcome

Four children in the study (2 aged 0–2 years) were prescribed GH. Twenty-one children have had renal transplants, of whom 86% eat and drink normally; 2 eat normally but need additional fluids via their gastrostomies and 1 still requires supplementary EF (the patient with the CHARGE association); 3 children were able to return to oral feeding without a change of treatment modality; 7 continue on EF, 2 were lost to follow-up and 2 died.

Discussion

This is the largest reported study of long-term supplementary EF in infants and young children with CRF. We have demonstrated that the introduction of EF promotes weight gain in children with moderate or severe and often deteriorating CRF and ESRF. This was particularly significant in the children starting EF before the age of 2 years, in whom the mean weight SDS was unchanged before EF and then increased consistently, supporting the findings of other studies [4, 5]. The older children showed less-severe failure to thrive prior to EF, but weight gain was then potentiated with EF. Weight was not disproportionate to height at the end of each child's study period, with only 3 of 35 having a body mass index greater than the 99.6th percentile [13].

There was significant catch-up growth at both the 1- and 2-year assessments after the introduction of EF in the 0 to 2-year age group who had previously been growing poorly despite standardised management of CRF by the same team. Although the children who started EF after the age of 2 years did not demonstrate a significant positive change in height SDS, they were able to maintain their height percentile. These results concur with the observations of Karlberg et al. [3] and Abitbol et al. [1] that growth is crucially nutrition dependent in the first 2 years of life.

There was no change in the assessed mean energy intake which did not exceed normal requirements in either age group throughout the study, contrary to the suggestion of Abitbol et al. [1] that additional energy to 125%–150% of RDA may be necessary for catch-up growth. However our study confirms the observation of both Rizzoni et al. [14] and Claris-Appiani et al. [5] in a small number of infants and young children that better growth can be achieved with an average energy intake of 100%–110% RDA. The mean percentage EAR in our study always exceeded the mean percentage RDA of 86% for children aged 1–3 years and 82% aged 4–6 years found by Foreman et al. [15] in a prospective observational study. The improved rate of weight gain without an increase in energy intake for age supports our clinical impression that feeds were more reliably delivered following the introduction of EF, and less feed was lost by vomiting. It is interesting to speculate that the abnormal foregut motility found in CRF may be circumvented by the slow continuous delivery of small feed volumes [16].

The percentage energy derived from the EF did not change with time in the 0 to 2-years group, despite their absolute energy intake increasing with age. These findings were similar in the older children and suggest that oral intake increased spontaneously in both age groups despite receiving EF. A significantly greater proportion of energy was derived from the feed at the start of EF in the 0- to 2-year-olds compared with the older children, as many of these infants would not have started weaning or had difficulties taking solids, as is common in CRF. However, the difference in the percentage energy from the feed between the 0 to 2-years and 2 to 5-year age groups became insignificant by 2 years, reflecting a more mature drinking and eating pattern with age unaffected by EF.

Tolerance of an increased concentration of fat in the feed was limited in all age groups and did not exceed an intake which might enhance hyperlipidaemia [17]. The non-protein energy content of the feed increased by 2 years and always exceeded 100 kcal/100 ml. The increments in carbohydrate concentration were well tolerated in all the children.

The protein intake in the conservatively managed children exceeded 100% of the RNI for protein throughout the study, and was higher in the older group who had a more protein-dense feed and also spontaneously ate more protein. However, the feed contributed less than the previously recommended 8% of energy derived from protein [18]. Although the percentage protein energy from the feed fell significantly in the 0 to 2-years group,

this reflects an increasing energy intake rather than a decrease in protein intake. This study shows that expressing protein as a percentage of energy intake can be misleading, as recognised by Uauy et al. [19] and protein intake in CRF should be prescribed according to actual body weight, as recommended for height age. It is reassuring that a more-generous protein intake can be prescribed without a detrimental effect on renal function, as the protein intake in our study was comparable to that deemed "low-protein" in the report of the European Study Group [20]. Although the protein intake in our study exceeded the RNI, the plasma urea remained below 20 mmol/l, as an adequate energy intake was provided. Plasma albumin, a simple marker of protein energy malnutrition, increased significantly during the study, supporting a finding of the European Study Group that serum albumin was the only significant biochemical parameter predicting height velocity at 1 year of age [21].

There was better control of secondary hyperparathyroidism as EF continued, which may have contributed to the improvement in linear growth. However Chan et al. [22] found no effect on the height SDS score of either calcitriol or dihydrotachysterol in previously untreated children with chronic renal insufficiency.

GH was prescribed in 2 children who started EF after the age of 2 years who, although they had gained 0.5 and 0.7 height SDSs by 2 years, remained below the 3rd percentile. Two children started GH under 2 years: 1 had shown some catch-up growth by 1 year (0.3 SDS) but was recruited into a GH trial; the second responded poorly to EF but also to GH, and there were concerns about compliance. Young children respond well to GH therapy [23], but the change in height SDS after 1 year is almost matched by EF for 1–2 years . Although the impressive growth rates demonstrated by Fine et al. [24] in children under 2.5 years establish a definite role for GH, as with EF there was a reduced response in the 2nd year of treatment.

The majority of the children who were subsequently transplanted ate normally, allaying an understandable anxiety expressed by Dello-Strologo et al. [25] that long-term EF precludes the development of normal eating habits. However, the process of re-establishing oral feeding may be difficult and the importance of positive early experiences are vital [26]. Children entering the study in the early years were fed by NGT unless a Nissen's fundoplication was indicated. More recently we have favoured the placement of PEGs or button gastrostomies recognising the advantages to both the child and family [27].

In this study of an unselected group of infants and young children with CRF/ESRF, nutritional intervention using EF has been shown to prevent or reverse weight loss and growth retardation, and in children less than 2 years of age significant catch-up growth can be achieved.

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LITERATURE ABSTRACTS

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A non-AUG-defined alternative open reading frame of the intestinal carboxyl esterase mRNA generates an epitope recognized by renal cell carcinoma-reactive tumor-infiltrating lymphocytes in situ

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A number of Ags recognized by tumor-reactive T cells have been characterized, including nonmutated geneproducts and a variety of epitopes shown to arise from either mutated or alternatively processed transcripts. Here, we report that the screening of a cDNA library with an HLA-B7-restricted renal cell carcinoma-reactive T cell clone derived from tumor-infiltrating lymphocytes (TILs) that were clonally amplified in vivo (as assessed by TCRBV complementarity determining region-3 length distribution analysis) resulted in the isolation of a nonamer encoded by an alternative open reading frame (ORF) (a +1 frameshift) of the intestinal carboxyl esterase gene. This peptide binds HLA-B*0702-presenting molecules as assessed in an immunofluorescence-based peptide binding assay using transfected T2 cells. Constitutive expression of this alternative ORF protein was observed in all transformed HLA-B7+ renal cell lines that were recognized in cytotoxicity assays by the TILs. The intestinal carboxyl esterase gene is transcribed in renal cell carcinoma tumors as well as in normal liver, intestinal, or renal tissues. Mutation of the natural ATG translation initiation site did not alter recognition, indicating that frameshifting (i.e., slippage of the ribosome forward) and recoding are not involved. In addition, a point mutation of the three AUG codons that may be used as alternative translation initiation sites in the +1 ORF did not abolish recognition, whereas mutation of an upstream ACG codon did, indicating that the latter codon initiates the translation of the alternative ORF. These results further extend the types of Ags that can be recognized by tumor-reactive TILs in situ (i.e., leading to clonal T cell expansion).

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Relationship between serum magnesium and parathyroid hormone levels in hemodialysis patients

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Acute magnesium (Mg) infusion decreases parathyroid hormone (PTH) secretion. However, the effect of chronic hypermagnesemia on PTH levels in dialysis patients is not well established. We studied 110 hemodialysis patients (mean age, 55 +/- 14 years; time on dialysis, 35 +/- 28 months) not receiving vitamin D and undergoing dialysis with an Mg dialysate concentration of 1.2 mg/dL. The primary phosphate binder was calcium carbonate, and 43% of the patients also needed aluminum hydroxide. During a 6-month period, calcium (Ca), phosphorus (P), and total serum Mg were measured every 2 months; intact PTH and aluminum (Al) were measured every 6 months. The mean value of each parameter was computed. Hypermagnesemia (serum Mg > 2. 47 mg/dL) was observed in 73% of the patients. Mg and Ca were inversely correlated with PTH levels (r = -0.48; $P < 0.001$ and r = -0.21; $P < 0.05$, respectively). After adjusting for Ca and P (partial correlation analysis), Mg and PTH were inversely correlated (r = -0.58; $P < 0.001$). A stepwise multiple regression analysis showed that PTH levels were predicted by Mg ($P < 0.001$), alkaline phosphatase ($P < 0.01$), and P levels ($P < 0.05$; multiple R = 0.57; $P < 0.001$), whereas Ca level, sex (dummy variable), diabetes (dummy variable), time on dialysis, and Al level were not predictive. Patients with inadequately low PTH levels (relative hypoparathyroidism, PTH < 120 pg/mL; n = 52) showed greater serum Mg concentrations than the rest (n = 58; 3.01 +/- 0.33 v 2.63 +/- 0.38 mg/dL; $P < 0.001$). In conclusion, serum Mg concentrations in dialysis patients are independently associated with PTH levels, suggesting that chronic hypermagnesemia may decrease PTH secretion and/or synthesis. In addition, chronic hypermagnesemia of dialysis patients may have a role in the pathogenesis of adynamic bone disease.